

The examination is being carried out on the **following application documents**

**Description, Pages**

1-74 as published

**Claims, Numbers**

1-75 as published

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure:

- D1 U. SCHWIETER, H. GUTMANN, H. LINDLAR, R. MARBET, N. RIGASSI, R. RÜEGG, S. F. SCHAEREN, O. ISLER: "Synthesen in der Carotinoid-Reihe 20. Mitteilung Neue Synthesen von Apocarotinoiden" HELVETICA CHIMICA ACTA, vol. 1, 1966, pages 369-390,
- D2 US 3 489 806 A (GUTMANN HUGO ET AL) 13 January 1970 (1970-01-13)
- D3 US 3 687 990 A (GUTMANN HUGO ET AL) 29 August 1972 (1972-08-29)
- D4 US 6 150 561 A
- D5 WO 03/072734 A2 (DIFFUSION PHARMACEUTICALS LLC [US]) 4 September 2003 (2003-09-04)
- D6 US 6 060 511 A (GAINER JOHN L [US]) 9 May 2000 (2000-05-09)
- D7 US 3 965 261 A (GAINER JOHN L) 22 June 1976 (1976-06-22)
- D8 US 4 046 880 A

1. Unity

1.1. The application lacks unity within the meaning of Article 82 EPC, since it includes five different inventions or groups of inventions:

- a) alternative method of synthesising TCS, and intermediates involved: claims 1, 49, 63 completely and claims 26-48, 50-62 partially.
- b) alternative Bipolar Trans Carotenoids, their salts; and method of preparing them: claims 2-7, 73-75 completely and claims 26-48, 50-62 partially.
- c) alternative formulations of trans-carotenoids: claims 8-25.
- d) alternative method for preparing trans-carotenoids: claims 26-48, 50-62 partially.
- e) alternative medical uses of trans-carotenoids: claims 64-72.

1.2. These inventions are only linked by the concept of Bipolar Trans Carotenoids, in the salt form or not, in particular Trans Sodium Crocetin (TSC). TSC and medical uses involving it, however, are known from D6 and D8 (abstract and column 4 of D6, abstract and lines 40-43 in column 2 of D8). Therefore, inventions a-e are not so linked to form a single general inventive concept.

1.3. In accordance with Rule 164(1) EPC the supplementary search report has been drawn up in those parts of the application which relate to the invention, or group of inventions, i.e. for claims 1, 49, 63 completely and claims 26-48, 50-62 partially.

The applicant is invited to limit the application to the invention covered by the European supplementary search report.

1.4. The subject-matter to be excised may be made the subject of one or more divisional applications. The divisional applications must be filed with the European Patent Office in Munich, The Hague or Berlin and shall be in the language of the proceedings relating to the present application (cf. Article 76(1) and Rule 36(2) EPC). The time limit for filing divisional applications (Rule 36(1) EPC) must be observed.

## 2. Novelty

2.1. D1-D3 disclose compound E (see compound 36 on page 375 of D1, example 11 of D2, and example 11 of D3). Therefore, claim 1 is not novel in the meaning of Art. 54 EPC.

2.2. D4 discloses diethyl crocetin ester and a method of synthesising it via a Wittig reaction involving a C<sub>10</sub> symmetrical dialdehyde and a triphenyl phosphonium chloride or bromide (see column 5 lines 8-10 and example 16) in the presence of sodium ethanolate. Consequently, claims 1, 50, 51, 53, 56-58, 60, and 61 do not meet the requirements of novelty of Art. 54 EPC.

2.3. D5 discloses a method of synthesising TSC in which a C<sub>10</sub> symmetrical dialdehyde is coupled with a C<sub>5</sub> Wittig reagent in benzene, before being saponified with NaOH in methanol (see scheme on page 25, and claims 26-32). Therefore, claims 26, 28, 29, 32, 33, 40, 41, 43, 48, 49, 50, 51, 54, 55, 60, and 62 do not meet the requirements of novelty of Art. 54 EPC.

### 3. Inventive step

3.1. D5 is the closest prior art. Claims 27, 31, 34-39, 44-47, 52 and 59 merely differs from D5 in the experimental conditions used for synthesising TSC or its diester precursor (solvent system used, saponification conditions, or Wittig reagent employed). Since TSC and its diester precursors are readily prepared in both the present application or D5, the problem to be solved is to provide alternative reaction conditions for the preparation of TSC.

3.2. The use of an alternative solvent system or the use of an alternative Wittig reagent cannot be seen as inventive, since the optimisation of the reaction conditions is a routine work for the skilled person and D4 already discloses the use of triphenyl phosphonium chloride or bromide (see column 5 lines 8-10 and example 16) and sodium ethanolate for the synthesis of diethyl crocetin ester. Likewise, the use of ethanol in combination with NaOH for the saponification step is suggested in D5 (claims 30 and 31). Consequently, claims 27, 31, 34-39, 44-47, 52 and 59 do not meet the requirements of inventiveness of Art. 56 EPC.

3.3. The preparation of crocetin as described in claim 63 does not involve an inventive step since crocetin is the free-acid form of TSC, i.e simple acidification of TSC leads to it.

#### 4. Clarity

4.1. Claim 26 is of the same category as claim 50 and possesses all the technical features of claim 50. It should therefore be drafted as dependent on it for matter of conciseness (Art. 84 EPC).

4.2. The terms "BTCS" in claim 26 and "BTC" in claim 44 have no meaning in the art, thus rendering unclear the exact scope of what is claimed (Art. 84 EPC).

4.3. The statement "C<sub>10</sub> or C<sub>20</sub> dial" in claim 28 is unclear since this can indicate the total number of carbon atoms or just the number of atoms of the main chain (Art. 84 EPC).

4.4. The term "pH neutral" in claims 29-31, and 51-53 is vague (Art. 84 EPC). Does it mean that the solvent system has a pH of 7 *exactly*, or a pH *around* 7 ?

4.5. The statements "C<sub>2</sub>, C<sub>3</sub>, C<sub>5</sub>, C<sub>10</sub> or C<sub>15</sub> Wittig ester" in claim 36, "C<sub>2</sub>, C<sub>3</sub> or C<sub>5</sub> phosphonoester" in claim 37 and "C<sub>5</sub> Wittig ester" in claim 57 are unclear since they can indicate the total number of carbon atoms or just the number of atoms of the main chain (Art. 84 EPC).

4.6. The vague and imprecise "incorporated by reference" statement in the description on pages 1, 2, 7, 10 and 24 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in a lack of clarity of the claims (Article 84 EPC) when the description is used to interpret the claims (see Guidelines C - III, 4.4). This statement should therefore be amended to remove this inconsistency.

4.7. The vague and imprecise "spirit and scope of this invention" statement in the description on page 28 implies that the subject - matter for which protection is sought may be different to that defined by the claims, thereby resulting in a lack of clarity of the claims (Article 84 EPC) when the description is used to interpret the claims (see Guidelines C - III, 4.4). This statement should therefore be amended to remove this inconsistency.

5. Other remarks

5.1. Drawings are present on pages 72-75 of the description, which is contrary to Rule 49(9) EPC.

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